U.S. Environmental Protection Agency
Science Advisory Board
Chemical Assessment Advisory Committee Augmented for the Review of the Draft IRIS Benzo[a]pyrene Assessment (CAAC-Benzo[a]pyrene Panel)

Public Teleconference
September 2, 2015

Minutes of the Meeting

Purpose: To continue discussion on the Science Advisory Board Panel's draft report on the EPA's *Toxicological Review of Benzo[a]pyrene (External Review Draft – September 2014)*

Meeting Participants:

CAAC-Benzo[a]pyrene Panel Members (See Roster):

Dr. Elaine Faustman, CHAIR
Dr. Ronald Baynes
Dr. Annette Bunge
Dr. Scott Burchiel
Dr. Anna Choi
Dr. John DiGiovanni
Dr. Joanne English
Dr. William Michael Foster
Dr. Helen Goeden
Dr. Sean Hays
Dr. John Kissel
Dr. Ed Levin
Dr. Abby Li
Dr. Maureen Lichtveld
Dr. Barry McIntyre
Dr. Bhagavatula Moorthy
Dr. Miriam Poirier
Dr. Kenneth M. Portier
Dr. Kenneth Ramos
Dr. Stephen Roberts
Dr. Richard Schlesinger
Dr. Leslie Stayner
Dr. Alan Stern
Dr. Charles Vorhees
Dr. Christi Walter

Other Attendees: see Attachment A.

Meeting Materials and Meeting Webpage:
The materials listed below may be found on the meeting webpage at:

https://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/EF7672F19493B8A185257E6C00557F57?OpenDocument

- Agenda
- Federal Register Notice
- Committee Members' Comments
    - Allometric Scaling Comments from Dr. Stephen Roberts
    - Chen et al. (2012) Statement, from Dr. Ed Levin
    - Comments from Dr. John DiGiovanni – Evidence for a Similar Mode of Action for BaP in Mouse and Human Skin

- Comments from Dr. John Kissel on the issue of the lack of an excess of skin tumors observed in most studies of therapeutic coal tar use
- Comments on the use of Gao et al. (2011) for Critical Endpoint, from Dr. Barry McIntyre
- Draft text to be inserted in Section 3.2.1. Developmental Toxicity, Developmental Neurotoxicity, from the Developmental Neurotoxicity Team
- Etiology of forestomach tumors in mice chronically fed Benzo[a]pyrene, from Miriam Poirier
- Rationale for recommendations to include Levin e al. (1977) and Nesnow et al. study (1983) study
- Response to EPA comments on Reproductive Toxicity
- Revised Paragraph to Epidemiologic Evidence of Skin Cancer

- Public Comments from James Roewer, Utility Solid Waste Activities Group

Meeting Summary:
The discussion followed the general plan as presented in the meeting agenda.

Opening Remarks
Dr. Wong convened the meeting and called the roll. All CAAC-BaP panel members were present except Drs. Bartell, and Gennings. Dr. Wong explained that the SAB CAAC-BaP panel operates under the authority of the Federal Committee Advisory Act (FACA). The SAB consists entirely of special government employees appointed by EPA to their positions. As government employees, all the members are subject to all applicable ethics laws and implementing regulations. She stated that for this SAB advisory activity, no conflict of interest or loss of impartiality issues were identified for any panel member.

Dr. Wong then turned the meeting over to Dr. Faustman, Chair of the CAAC-BaP Review Panel. Dr. Faustman reviewed the agenda and led the panel to continue discussion of the draft report.

Panel Discussion of the Draft SAB Report:

Section 3.3.5. Dermal Slope Factor
Dr. Faustman called on the following panel members to present their writing assignment for panel discussion:

a. Dr. Annette Bunge presented her write up to clarify the SAB's recommendations that Nesnow et al. (1983) and Levin et al. (1977) should be included in Table 2-11 of the draft assessment. Her comments can be found on the meeting webpage.
b. Dr. John Kissel presented his write up that explained the lack of an excess of skin tumors observed in most studies of therapeutic coal tar use. There is a large body of literature that shows psoriatic skin is not normal skin, and proliferates and shed much more rapidly than normal skin. In addition, the clinical studies involving the use of coal tar are incomplete. The limitations of these studies, and the nature of psoriatic skin, make the available data largely uninformative with regard to the question of whether BaP induces skin cancer in humans. His write up can be found on the meeting webpage.

c. Dr. Anna Choi presented a revised paragraph noting that EPA review of the epidemiologic evidence of skin cancer in humans was not sufficiently thorough. Additional references on occupational exposure studies were provided.
d. Dr. John DiGiovanni presented his write up on evidence for a similar mode of action for BaP in mouse and human skin. There is reasonable evidence that BaP is metabolically activated to diol-epoxides leading to formation of DNA adducts in mouse and human. The formation of DNA adducts leads to mutation that represents an initiating event for tumor development. His write up can be found on the meeting webpage. Dr. Faustman asked if a sentence that referred to the lung, and other tissue could be added. Dr. Giovanni commented that additional studies have investigated other tissues, and a sentence could be added (with references) for other tissues.

The panel then discussed Dr. Miriam Poirier's write up on the etiology of forestomach tumors in mice chronically fed BaP for Section 3.2.4, Cancer. The panel discussed the mode of action of the forestomach tumors, in response to Dr. Mike Dourson's comments on non-linearity during the August 21 panel teleconference. Dose-response relationship was shown for the formation of BPdG, the major stable mutagenic DNA adduct induced by BaP, in forestomachs of mice fed BaP for 21 days at 5 different dose levels. A panel member commented that the mouse forestomach stratified epithelium is similar to that of skin, and the phenomenon of rodent forestomach tumors induced by oral BaP exposure is considered to proceed via mechanisms similar to those in skin. In the forestomach, hyperplasia of the squamous epithelial cell layer plays a role. However, the panel agreed the presence of hyperplasia does not preclude a mutagenic MOA, particularly in the face of abundant evidence of DNA damage, but may contribute to an enhancement of tumor incidence. Because BaP is a complete carcinogen, the mechanism of action must include both the initiating (mutagenic) and the promoting effects. The panel agreed that a linear extrapolation from the point of departure is the appropriate approach for estimating the cancer potency of BaP, the observation of hyperplasia notwithstanding. This paragraph on forestomach tumor will be revised to strengthen this concept.

Section 3.3.1 Oral Reference Dose

The panel agreed neurodevelopmental endpoints are in principle an appropriate basis for deriving an RfD. However, the panel agreed EPA should consider including their rationale to support either inclusion or exclusion of endpoints for RfD determination.

Dr. Barry McIntyres presented his write up on the potential use of cervical hyperplasia and cervical inflammation from Gao et al. (2011) as a critical endpoint to address EPA's comment if cervical hyperplasia or inflammation is directly related to impaired reproductive function.

Dr. Ed Levin presented his write up to address public comments and EPA response to whether decreased anxiety-like effects in elevated plus maze are adverse effects. Decreased anxiety represents a persistent behavioral change caused by developmental BaP exposure that is significantly different from control behavioral change. Given that BaP induced behavioral changes in other behavioral tests, the results of Chen et al. (2012) provide converging evidence that shows a consistent pattern of alterations caused by developmental BaP exposure that can be seen from early development to adulthood that may be irreversible.

The panel then discussed the uncertainty in available data. Dr. Vorhees presented his write up on neurodevelopmental toxicity data gap in brain development. These gaps should be considered by the EPA in the overall evaluation of BaP developmental neurotoxicity. The panel then had lengthy discussion on EPA's application of a database uncertainty factor of 3. Dr. Alan Stern proposed he would gather input from the panel and rewrite the paragraph on database uncertainty.

Section 3.2.3 Immunotoxicity
The panel then discussed the Immunotoxicity section. The panel agreed to delete "one to two orders of magnitude" on the sentence on Pg 17, line 45, so that the sentence will read "It is likely that the developing immune system may be more sensitive to BaP exposures than adult exposures…" For recommendations, the panel agreed to delete the first bullet on sensitive immune function endpoints are not available; and the last bullet on woodsmoke inhalation studies. A new bullet on associations between immunologically relevant endpoints and BaP adducts have been found in some human birth cohort studies will be added.

Section 3.2.2 Reproductive Toxicity

Dr. Christie Walter presented her write up to address EPA's comments on which additional ovarian and testicular effects/studies should be considered, and also EPA's comments on the recommendation regarding the studies or parts of studies brought forward for dose-response analysis.

Section 3.3.3 Oral Slope Factor for Cancer

Dr. Stephen Roberts presented his write up on allometric scaling that will be added to the text for dose-response analysis in this section. Dr. Faustman suggested that allometric scaling is a concern for other routes of exposure and this write up should be extended to other routes. Drs. Alan Stern and Stephen Roberts were assigned to this task.

Section 1.0 Executive Summary
The executive summary would be revised based on changes to the individual sections.

Letter to the Administrator
A sentence should be added to state the SAB agrees that BaP-induced tumors primarily through a mutagenic mode of action resulting from BaP-induced DNA damage.

Appendix C

The panel had no comments on Appendix C

Brief Public Comments

Dr. Anne LeHuray made a clarifying remark that it is her understanding that EPA/IRIS has access to and may consider results of comparable studies submitted as part of FIFRA registrations. These studies are not usually published, but are available to EPA and perhaps other researchers. It's been brought to her attention that a radiolabeled dermal absorption study in rat and human skin was submitted to and

accepted by EPA as part of the creosote FIFRA registration. Creosote is another PAH-containing substance. Dr. Cogliano said he will look into this.

Dr. Faustman turned the meeting over to the DFO. Dr. Wong reviewed the next steps for the panel. Dr. Faustman noted that there were several issues that required further work from the panel. Panel members would work in teams to finish revising the text. The revised report will be circulated to the panel for concurrence. Dr. Faustman and Dr. Wong thanked all the participants and adjourned the teleconference around 4:30 pm.

On Behalf of the Committee,
Respectfully Submitted,

_____/s/_____
Diana Wong, Ph.D.
Designated Federal Officer

Certified as Accurate:

_____/s/_____
Elaine Faustman, Ph.D.
Chair, SAB CAAC-Benzo[a]pyrene Review Panel

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Attachment A. Other Attendees

List of persons who identified themselves on the teleconference or who had requested call-in-information for the meeting.

Name	**Affiliation**
Vince Cogliano	EPA
Samantha Jones	EPA
Kathleen Newhouse	EPA
Ann LeHuray	Pavement Coating Technology Council
David Reynolds	Inside EPA
Julie LeMay	Gradient
Nancy Beck	American Chemistry Council
Rayna Laiosa	PSEG
Maggie Fawal	Utility Solid Waste Group
Leeann Sinagoga	Tetratech
Roxana	FDA
Fred Reitman	Shell
Jim Rollins	Policy Navigation Group
Pamela Lamie	CDM Smith